UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF PREVENTION, PESTICIDES, AND TOXIC SUBSTANCES
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MEMORANDUM

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SUBJECT: Response to Registrant Comments on Chlorpropham TRED.

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This memo responds to comments on the chlorpropham TRED by Ralph I. Freudenthal, Ph.D., in a letter dated June 17, 2002.

Registrant Comment: Need for a cumulative risk assessment.

"In its reassessment of the chlorpropham tolerance, the Agency states that the risk from ingesting 3-chloroaniline (3-CA) should be determined using the same cancer potency factor as 4-chloroaniline (4-CA). The Agency's decision is based only on a structure-activity relationship, since cancer tests for 3-CA have not been conducted. While the April comments from Pin/Nip on the draft chlorpropham TRED document suggest that this theory may be incorrect, the Agency's present policy requires that a cumulative risk assessment be performed to address dietary exposure from all chemicals which the Agency assumes share the 4-CA cancer potency (Q1*). This includes at least 4-CA, 3-CA, and 4-chlorophenylurea (4-CPU). Based on the requirements of the Food Quality Protection Act (FQPA), the Agency cannot reassess the chlorpropham tolerance *until this cumulative risk is addressed*."

".... Additionally in the Diflubenzuron Reregistration Eligibility Document (RED, see attached Fact Sheet), the Agency states that 4-CA is a metabolite of Diflubenzuron and a second metabolite, 4-CPU is closely related to 4-CA and should be considered as having the same cancer potency as 4-CA. The Agency has calculated a cancer dietary risk from the diflubenzuron metabolites 4-CA and 4-CPU as approximately $1x10^{-6}$. As the Agency is stating that these three chemicals have the same nature and mechanism of toxicity, it is obligated to address the FQPA factors, including an assessment of the cumulative effects from exposure to the three chemicals, utilizing the two identified exposure estimates and all other non-occupational exposure in EPA files (for example the possible degradation of linuron to 4-CA in soil)."

".... By publicly asserting that 4-CA, 3-CA, and 4-CPU are related structurally, and by assessing them using the same cancer potency factor, the Agency has made a *de facto* decision that these substances share a common mechanism of toxicity. Therefore, under existing law, the FQPA factors must be addressed by the Agency to put into perspective the propose human cancer risk, *prior* to readdressing the chlorpropham tolerance."

HED Response:

The response to the registrant's argument that 3-CA should not be classified as a carcinogen were addressed in a previous memo (Danette Drew and Kit Farwell, 5/13/02).

References to 3-CA and 4-CPU in the Diflubenzuron R.E.D. Fact Sheet were from a Metabolism Assessment Review Committee meeting which was held to determine the risk assessment process for Diflubenzuron and was not intended to address the need for a cumulative cancer risk assessment.

As noted in "Guidance for Identifying Pesticide Chemicals and Other Substances That Have a Common Mechanism of Toxicity" (January 29, 1999), the Agency is currently developing a process for performing cumulative risk assessments.

As the Agency develops a process for performing cumulative risk assessments, the need for a cumulative risk assessment for these metabolites may be re-evaluated in the future, but is not needed now because cancer risk from 3-CA is expected to overestimate the risk. As noted in the Chlorpropham risk assessment, "... substitution in the meta position (3) is not likely to cause increased potency. Therefore, the use of the Q_1* from a para substituted aniline (4-CA) to estimate cancer risk from a meta substituted aniline (3-CA) is expected to overestimate the risk."

The Agency has taken the conservative position that a cancer risk assessment for 3-CA in potatoes is needed because of structure-activity concerns, and has characterized that risk by using the language in the previous paragraph.

The most appropriate way to determine the carcinogenic potential of 3-CA is to conduct carcinogenic studies in rodents with 3-CA. In the absence of these carcinogenicity studies, the cancer risk to humans for 3-CA can only be estimated using the Q1* for 4-CA of 1.12×10^{-1} based on male mouse liver adenoma and/or carcinomas.

Registrant Comment: Value of correct Q1*.

"It appears that the Agency has used an incorrect Q1* value in its calculation of the cancer risks. While in the RED a Q1* of 0.068 was used to calculate the 1.3×10^{-6} dietary risk from 3-CA, the EPA Chemicals Evaluated for Carcinogenicity Potential table, dated March 12, 2002, shows a Q1* for 4-CA of 0.112 ...."

HED Response:

The correct value for the Q1* of 4-CA is 1.12×10^{-1} based on male mouse liver adenoma and/or carcinomas (6/14/01 memo from Lori Brunsman, Doc. No. 014583). The risk assessment for chlorpropham should be revised using this Q1* value.